Population Pharmacokinetics and Exposure-Response Analyses of Navepegritide in Children With Achondroplasia

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Introduction

Achondroplasia (ACH), a rare genetic condition arising from a systemic fibroblast growth factor receptor 3 (FGFR3) variant and which leads to skeletal dysplasia and serious muscular, neurological, and cardiorespiratory complications, affects more than 250,000 people worldwide.[1,2]

In bone, FGFR3 acts as a negative regulator of chondrocyte differentiation. The constitutive activation of FGFR3 in ACH and the subsequent sustained downstream signaling results in poor endochondral bone growth and skeletal dysplasia.[1,3,4] C-type natriuretic peptide (CNP) is a positive regulator of bone growth that promotes chondrocyte differentiation by inhibiting the FGFR3 signaling pathway.[1,5,6]

Navepegritide is a prodrug of CNP that is administered once weekly (q1w) and is designed to provide sustained release and continuous systemic exposure to active CNP to counteract the constitutively active FGFR3.[5] Navepegritide is approved by the FDA to increase linear growth in children aged 2 years and older with ACH with open epiphyses.[7]

Navepegritide is designed to avoid high peak plasma concentrations of active CNP to prevent the acute hypotensive effects observed historically with administration of exogenous CNP.[8,9] Navepegritide consists of a CNP moiety identical to the amino acid sequence 89-126 of endogenous CNP transiently linked to an inert methoxypolyethylene glycol (mPEG) carrier via a proprietary TransCon® linker **(Figure 1)**.

A semi-mechanistic pharmacokinetic (PK) model of navepegritide has previously been developed using data from 35 healthy adults and 42 children with ACH.[10]

Objectives

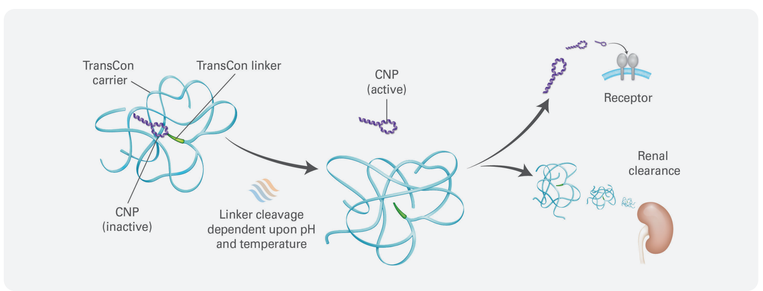
- Strengthen the existing PK model with data from 90 additional children and adolescents with ACH treated with navepegritide and perform external validation with data from 40 children and infants with ACH treated with navepegritide, and use the model to evaluate a simplified navepegritide dosing scheme according to weight-based dose bands
- Explore the active CNP exposure in infants (< 2 yr) compared to children (≥ 2 yr to < 18 yr)
- Explore the relationship between active CNP exposure and annualized growth velocity (AGV)

Conclusions

Navepegritide PK in infants, children, and adolescents with ACH was well-characterized by the semi-mechanistic model, showing similar and sustained release of active CNP across age groups and avoidance of high peak plasma concentrations.

Findings from the PK model, together with the identified relationship between active CNP exposure and AGV, provides strong supporting evidence for 100 µg/kg/week as the appropriate therapeutic dose of navepegritide. Further, simulations with the PK model support the use of weight-based dose bands with the aim of simplifying dose administration.

Figure 1: **Navepegritide (TransCon® CNP)**



Methods

Data and Model Development

- Steady state PK of CNP released from navepegritide (released CNP), total CNP, and mPEG were characterized in the population PK model based on data from children with ACH and healthy adults.

Methods

- The starting point for model development was the previously reported PK model[10] based on data from a Phase 1 trial in healthy volunteers (n = 35)[11], two Phase 2 trials (n = 57,[12] n = 24[13]) and a pivotal trial in children with ACH aged 2-11 years at screening (n = 84),[14] and an open-label extension trial (n = 39).[15] The model was updated using additional long-term data for some of these participants, and subsequently validated with long-term extension data and externally validated using data from a total of 40 participants (33 children aged ≥ 2 years with ACH who switched from placebo to open-label treatment with navepegritide,[13,14] and 7 infants aged 0 to < 2 years with ACH).[16]
- The dose-ranging phase 2 trials evaluated subcutaneous doses of navepegritide 6, 20, 50 or 100 µg/kg q1w. The pivotal and open label extension trials evaluated navepegritide 100 µg/kg q1w.
- The 3 analytes measured in the clinical trials were:
  - **Released CNP**: free CNP released from navepegritide; identical to the 89-126 C-terminal amino acid sequence of human CNP
  - **Total CNP**: CNP bound in the prodrug (navepegritide) including negligible contributions from released CNP and endogenous CNP; total CNP is a measure of the navepegritide concentration
  - **mPEG**: total mPEG, including mPEG bound in the prodrug (navepegritide) and released mPEG
- The covariate analysis included time-varying body weight, renal function, sex, race and ethnicity, with dose evaluated separately. Covariates were either considered to be mechanistic and included in the model without statistical testing or tested using a stepwise covariate modeling (SCM) approach.

Exposure-Response Analysis

- The exposure-response analysis was conducted by pairing model-predicted individual $AUC_{\tau,ss}$ of released CNP and AGV at Week 52. Model evaluation included linear, E_{max}, and sigmoidal E_{max} models. Exposure following dosing according to weight-based dose bands was simulated and compared to the model-predicted exposure of the participant dosed according to weight-based dose bands.

Results

Navepegritide Population PK Model

- The navepegritide population PK model **(Figure 2)** was consistent with the previously reported model.[10]
- The model described the 3 analytes (released CNP, total CNP, and mPEG) in subcutis and plasma, with first-order absorption from subcutis and first-order elimination from blood. Only released CNP was implemented as an explicit compartmental state variable in the structural model; total CNP and mPEG were defined as algebraic functions of the released CNP state variable.
- Navepegritide releases CNP in both subcutis and plasma via auto-cleavage of the TransCon Linker, as dictated by the TransCon Linker release rate (k_{rel}).
- Time-varying body weight was the only clinically relevant covariate identified in the analysis. The model accurately described the characteristics of the validation dataset.

Steady State PK in Infants, Children, and Adolescents With ACH

- Individual parameter estimates from the population PK model were used to predict concentration versus time profiles of released CNP **(Figure 3)**. During q1w dosing, the administration of navepegritide provided sustained release and continuous exposure to active CNP avoiding high peak plasma concentrations, thereby reducing the risk of acute hypotensive effects.

Figure 2: **Navepegritide Model Structure**

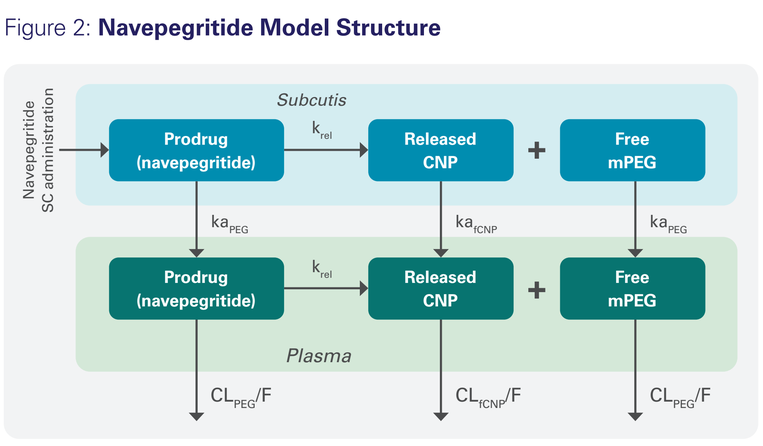
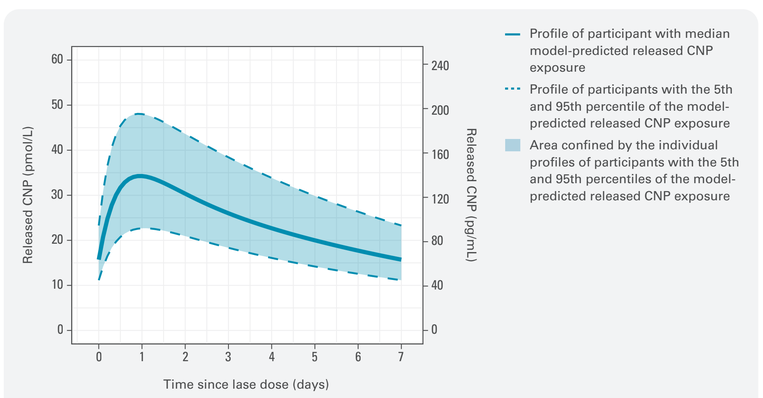


Figure 3: **Profile of Released CNP Concentration at Steady State Over a 1-Week Dosing Period**

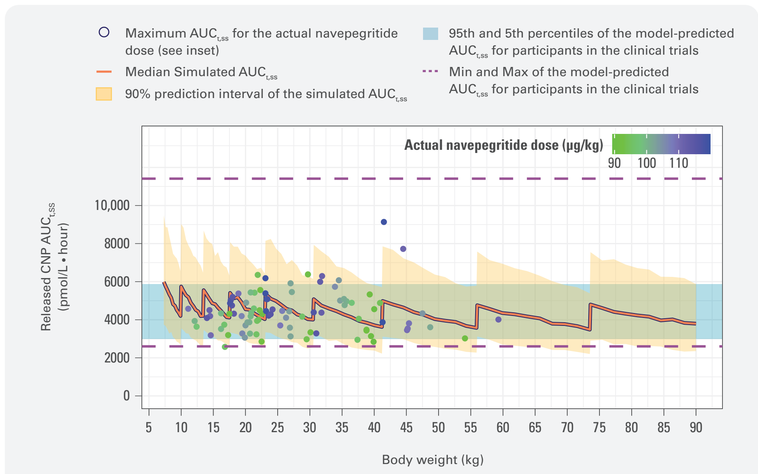


Note: Predicted steady-state released CNP concentration–time profiles following navepegritide 100 µg/kg q1w. Individual steady-state profiles were predicted using Empirical Bayes Estimates from the population PK model for trial participants receiving navepegritide 100 µg/kg/week.

Dosing According to Weight-Based Dose Bands

- During clinical development, navepegritide dosing was weight-based and specified in the unit of µg/kg. Dose bands were designed to simplify dose administration for the prescriber, patient, and caregiver, while achieving an overall similar navepegritide exposure to that observed in the clinical development program at the once-weekly dose of 100 µg/kg.
- **Figure 4** depicts simulations of released CNP $AUC_{\tau,ss}$ by body weight following dosing according to weight-based dose bands in children and adolescents with achondroplasia:
  - The dose in µg/kg is approximately 100 µg/kg at the body weight midpoint of each dose band. Thus, patients with body weights at the lower and upper end of a given dose band will receive a slightly higher or relatively lower µg/kg dose, respectively. As patients grow, they will transition through the dose bands and will thereby receive doses across the entire dose range, some of which will be slightly lower than the target dose of 100 µg/kg/week and some will be slightly higher. The proposed weight-based dose bands provide sufficient exposure of released CNP to ensure a satisfactory treatment response.

Figure 4: **Simulations of Released CNP $AUC_{\tau,ss}$ by Body Weight Following Dosing According to Weight-Based Dose Bands in Children and Adolescents With Achondroplasia**

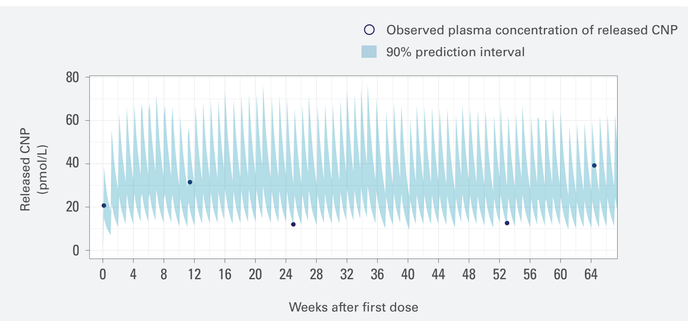


Note: The simulated $AUC_{\tau,ss}$ (yellow ribbon) were calculated during the 26th week of dosing (assuming q1w dosing) for 10 given body weights within each dose band. The model-predicted $AUC_{\tau,ss}$ (blue ribbon) was calculated based on the Empirical Bayes Estimates for the participants in the clinical trials who received 100 µg/kg/week. Each point represents the maximum $AUC_{\tau,ss}$ during the period (maximum 6 months), where the participants were dosed according to weight-based dose bands in open label extension trial.

PK in Infants With ACH

- Model simulations of released CNP concentrations following dosing in infants with achondroplasia **(Figure 5)** are comparable to observed plasma concentration of released CNP in children aged 2 years and above.

Figure 5: **Model Simulations of Released CNP Concentrations Following Dosing of 100 µg/kg Once Weekly in Infants With Achondroplasia**

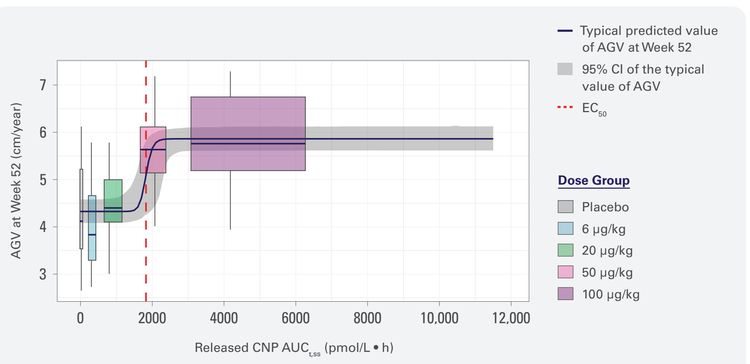


Note: Model simulation for an infant with ACH with baseline age and body weight of 4 months and 6.0 kg, respectively. The dosing history for the infant was used in the model simulation. The prediction interval is based on 1000 replicates.

Exposure-Response Analysis

- The relationship between released CNP $AUC_{\tau,ss}$ and AGV at Week 52 was best described by a steep sigmoidal-shaped E_{max} model **(Figure 6)**, with an EC_{50} of approximately 2000 pmol/L*h (red dashed line on chart).
- All participants receiving navepegritide 100 µg/kg/week were predicted to have $AUC_{\tau,ss}$ above approximately 2000 pmol/L·h.
- AGV increased with increasing exposure of active CNP and reached a plateau at the steady-state exposure level achieved with navepegritide 100 µg/kg q1w.

Figure 6: **Exposure-Response Model of AGV at Week 52 vs Released CNP Exposure in Children With ACH**



Note: Box plots depict observed AGV and predicted released CNP $AU_{\tau,ss}$ for each dosing group. Vertically, the boxes are bounded by the 25th and 75th percentiles of the observed AGV per dose group, the solid line inside the boxes represents the median and the whiskers extend to the 5th and 95th percentiles. Horizontally, the width of the box represents 90% of the $AUC_{\tau,ss}$ data per dose group and the whiskers intersect the median. Simulated AGV at Week 52 is depicted by the solid black line representing the typical value and the grey ribbon depicts the 95% CI around the typical value. The red dashed line marks the $AUC_{\tau,ss}$ resulting in half of the maximum increase in AGV.

Abbreviations

$AUC_{\tau,ss}$ = area under the curve from time 0 to time tau (the dosing interval) at steady state; **CL_{fCNP}/F** = apparent clearance for released CNP; **CL_{PEG}/F** = apparent clearance for navepegritide and mPEG; **CNP** = C-type natriuretic peptide; **E_{max}** = maximum effect; **EC_{50}** = half maximal effective concentration; **FDA** = Food and Drug Administration; **FGFR3** = fibroblast growth factor receptor 3; **GFR** = glomerular filtration rate; **ka_{fCNP}** = first-order absorption rate constant for Released CNP; **ka_{PEG}** = first-order absorption rate constant for navepegritide and mPEG; **k_{rel}** = TransCon Linker release rate; **mPEG** = methoxy polyethylene glycol; **NPR-B** = natriuretic peptide receptor B; **PK** = pharmacokinetic; **q1w** = once weekly; **SC** = subcutaneous; **SCM** = stepwise covariate modeling; **V_{fCNP}/F** = apparent volume of distribution for released CNP(89-126); **V_{PEG}/F** = apparent volume of distribution for navepegritide and mPEG

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